EXHIBIT A

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UNITED STATES DISTRICT COURT

WESTERN DISTRICT OF TEXAS

LEANNE SPARLING and MICHAEL J. SPARLING, on behalf of and as representatives for MICHAEL L. SPARLING, deceased, **Plaintiffs,** **v.** **USPLABS, LLC, JONATHAN VINCENT DOYLE (an individual), JACOB GEISSLER (an individual), USPLABS JACK3D, LLC, USPLABS HOLDING, LLC, GNC CORPORATION, NATURAL ALTERNATIVES INTERNATIONAL, INC., and DOES 1-500, Inclusive,** **Defendants.**	**Case No.: 3:13-cv-00323-DCG** **PLAINTIFF'S OBJECTION TO ORDER OF ANNE T. BURTON DATED JULY 27, 2015 (DOCKET #: 331)**

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I. INTRODUCTION

On July 27, 2015, the Hon. Mag. Judge Anne T. Berton granted Defendants' Motions to Strike the testimony of Dr. Louis Cantilena, Dr. Daniel Rusyniak and Dr. Edward Mills. (ECF#184, 186, 187, 331.)[1] Plaintiffs' experts, including two of the foremost researchers on hyperthermia in the world and one of the leading pharmacologists/toxicologists working with the FDA, have offered opinions that DMAA is capable of causing hyperthermia based on a mountain of evidence, including pharmacological studies on DMAA, numerous peer-reviewed human studies on DMAA, textbooks and basic pharmacological and toxicological principles. Despite this evidence, the Magistrate made several errors, including failing to consider critical party admissions on the mechanism of action and ultimate causation, viewing each part of the opinions without viewing them as a whole thereby missing several bridges from the data to the opinions, conflating mechanism of action with class effect, making independent factual determinations of issues not in dispute and other errors as discussed herein. Thus, Plaintiffs respectfully request this Court overrule the Magistrate's Order.

II. ARGUMENT

Upon proper objection, a District Court is required to modify any part of a magistrate's non-dispositive order that is "clearly erroneous or is contrary to law." Fed R. Civ. P. 72 (a). Under this standard, a magistrate judge's factual determinations are overturned "only if the court reaches a 'definite and firm conviction that a mistake has been committed.'" *Perry v. Schwarzenegger*, 268 F.R.D. 344, 348 (N.D. Cal. 2010). Legal conclusions, however, are "reviewed de novo to determine whether they are contrary to law." *Id*. The Supreme Court has held that admissibility of testimony pursuant to Fed. R. Evid. 702 is a conclusion of law, as

[1] Plaintiffs do not object to the Magistrate's Order to the extent it denied the Motion to Strike the testimony of Dr. Mahmoud El Sohly. (ECF#185.)

opposed to fact. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 143, 118 S. Ct. 512, 517, 139 L. Ed. 2d 508 (1997) ("admissibility of expert testimony is not [] an issue of fact ."[2]). Accordingly, July 27, 2015 Order which denied the admissibility of expert testimony is reviewed de novo.[3]

A. Plaintiffs' Experts' Opinions that DMAA is Capable of Causing Hyperthermia is Based on Considerable Evidence and Reliable Methodologies

Plaintiffs' experts are distinguished, highly qualified and at the top of their fields.[4] Dr. Cantilena, Dr. Mills and Dr. Rusyniak have each opined that DMAA is capable of causing hyperthermia and death.[5,6] The core of the opinions is that DMAA is established with peer-reviewed data to be an alpha-agonist causing vasoconstriction (that is, it stimulates the alpha receptors in the skin causing the skin to vasoconstrict and reduce blood flow to the skin thereby increasing core body temperature.) This is the exact same mechanism which is generally accepted to cause hyperthermia in other sympathomimetics. And furthermore, the amount of DMAA found in Sparling's blood was compared to the level of epinephrine actually causing cutaneous vasoconstriction and increased heat therefrom in exercising humans. This provided confirmation of the mechanism of action at the dose of DMAA to which Sparling was exposed.

Much has been made about whether Plaintiffs' experts are merely offering an opinion

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[2] Although the *Joiner* Court applied an "abuse of discretion" standard, this was done in the setting of an appeal court's review of a district court order. A less deferential standard of review applies in the current situation where a magistrate judge is reviewed by a District Court judge.
[3] Out of respect for the Court's time and resources, and mindful of the extensive briefing thus far, Plaintiffs try not to reiterate too much of their arguments which are already in the record.
[4] ECF#276-22, Cantilena Rep. at ¶¶ 1-6; ECF#276-27, Rusyniak Rep. at ¶¶ 1-2; ECF#276-25, Mills Rep. at ¶¶ 1-2.
[5] ECF#276-24, Mills Dep. at 121:21-122:1; ECF#276-4, Cantilena Dep. at 45:24-46:25, 99:13-100:101:7, 131:25-132:11, 45:24-46:25, 99:13-101:7, 56:1-9, 59:2-4; ECF#276-26, Rusyniak Dep. at 21:1-3.
[6] Although Plaintiffs also object to the Magistrate's exclusion of the specific causation opinions since those were excluded based on the exclusion of the general causation opinions, Plaintiffs reserve argument on this particular issue other than to cite to the extensive differential diagnosis performed by Dr. Cantilena. (ECF#323, Hr'g Tr. at 43:16-51:11.)

based on class effects. It is true the opinions start with the generally accepted fact that certain sympathomimetics increase blood pressure and cause heat stroke (e.g., MDMA- aka ecstasy-, cocaine and amphetamine).[7,8] The mechanism by which those sympathomimetics increase blood pressure is through activation of the alpha receptors which causes vasoconstriction.[9] They also activate alpha receptors in the skin causing reduced circulation of blood in the layers of the skin by the physiological mechanism of cutaneous vasoconstriction.[10] This cutaneous vasoconstriction, which limits the flow of blood to the skin, interferes with the dissipation of heat from the muscles.[11] This is the mechanism by which sympathomimetics known to cause hyperthermia operate.[12]

DMAA, another sympathomimetic, has been shown in randomized, placebo-controlled, peer-reviewed human clinical trials with statistically significant results to use the same mechanism of action: **cutaneous vasoconstriction (vasoconstriction in the skin)**.[13] So too has

[7] An opinion not contradicted by the Defendants' experts or any other evidence in the record.
[8] ECF#276-22, Cantilena Rep. at ¶ 15; ECF#276-27, Rusyniak Rep. at ¶¶ 4-5; ECF#276-25, Mills Rep. at ¶¶ 5-13; ECF#277-34, Knochel chapter at p.1563; ECF#277-18-20, Westfall chapter at p.282; ECF#277-38, Rosen chapter at pp.2124-25; ECF#277-39, Winkenwerder chapter; ECF#277-40, Marsha chapter.
[9] *Id.*
[10] *Id.*; ECF#277-17, Drummond; ECF#277-18-20, Westfall at p.281; ECF#276-28, Coyle Rep. at ¶ 23.
[11] ECF#277-34, Knochel chapter; ECF#276-26, Rusyniak Dep. at 118:1-19; ECF#276-22, Cantilena Rep. at ¶ 15; ECF#276-25, Mills Rep. at ¶¶ 5-6; ECF#277-29, Kurtz.
[12] ECF#276-26, Rusyniak Dep. at 112:16-113:4, 111:1-119:5; ECF#276-22, Cantilena Rep. at ¶ 15; ECF#276-25, Mills Rep. at ¶¶ 5-12; ECF#276-27, Rusyniak Rep. at ¶¶ 4-5; ECF#276-4, Cantilena Dep. at 135:22-136:15; ECF#277-38, Rosen chapter at pp.2124-25; ECF#277-39, Winkenwerder chapter; ECF#277-40, Marsha chapter; ECF#277-18-20,Westfall chapter at p.283.
[13] ECF#277-14, Marsha; ECF#277-15, Marsh; ECF#277-32; Swanson; ECF#277-12, McCarthy; ECF#277-11, Farney; ECF#277-13, Bloomer; ECF#276-4, Cantilena Dep. at 80:21-81:11; ECF#276-22, Cantilena Rep. at ¶ 8; ECF#276-27, Rusyniak Rep. at ¶¶ 4-5; ECF#276-26, Rusyniak Dep. at 104:24-105:6.

DMAA been shown to increase body heat as a result.[14] And the peer-reviewed human studies showing that DMAA increases heat also show a dose-response; that heat increases with higher systemic exposure.[15] This is the bridge. DMAA is not just a sympathomimetic, it acts in the exact same way that other sympathomimetics do when they cause hyperthermia.

The experts have confirmation that the mechanism of action does not just theoretically cause vasoconstriction and increases in core body temperature it actually does so in exercising humans.[16] In order to account for the differences in potency between epinephrine (the drug used in the Coyle study which measured cutaneous vasoconstriction and body temperature after administration of the sympathomimetic) and DMAA a calculation was made using an accepted pharmacoequivalence conversion given the known relative potencies between epinephrine and DMAA.[17] By using the relative potencies (amount of drug effect per dose) Dr. Cantilena was able to reliably compare the cutaneous vasoconstriction and increased heat caused by epinephrine in the Coyle study to the DMAA found in Sparling as confirmation of the mechanism of action at the dose of DMAA to which Sparling was exposed.[18]

Of course, exposure to DMAA does not cause heat stroke in every person who takes it, there are susceptible individuals.[19] The available clinical studies support the fact that certain persons are susceptible to the vasoconstrictive sympathomimetic properties of DMAA.[20] However, such susceptibility is not necessary to explain Private Sparling's death.

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[14] ECF#276-22, Cantilena Rep. at ¶ 15; ECF#276-24, Mills Dep. at 48:20-24, 58:22-59:2, 81:7-13, 87:19-22.-89:24.
[15] ECF#327-22-25, Mills Supp. Report.
[16] ECF#277-27, Gonzalez; ECF#277-23, Coyle Rep. at ¶ 27; ECF#276-4, Cantilena Dep. at 98:16-101:7.
[17] ECF#323, Hr'g Tr. at 12:22-17:7, 124:10-125:1, 133:2-135:2,126:25-127:10.
[18] *Id.*
[19] ECF#196-5, Cantilena Dep. at 160:22-161:25, 262:15-263:9.
[20] *Id.*

The general causation opinions at issue are based on statistically significant peer-reviewed, clinical studies of humans ingesting DMAA at comparable doses to Jack3d, accepted pharmacological and toxicological principles and facts from textbooks, pharmacological studies in the development of DMAA by Eli Lilly, and pharmacokinetic studies. This is not the case in which the experts know little about the drug other than its chemical structure or extrapolate from data using large doses in animals.[21] The methodology used above for making determinations of causality is accepted within the toxicological community and specifically embraced by the FDA in making safety determinations about drugs and dietary supplements[22]as well as the Institute of Medicine.[23] So too has the Reference Manual on Scientific Evidence (3rd Ed.), 679 found the methodology of using biological plausibility reliable.

Using the *Daubert* factors, although not required, also illustrates the reliability of Plaintiffs' experts' methodology: 1) testability: the Coyle study confirms that alpha-agonist sympathomimetics cause cutaneous vasoconstriction and increased core body temperature, 2) peer review: The Memphis peer-reviewed studies confirm that DMAA is an alpha-agonist sympathomimetic that causes vasoconstriction, that it increases metabolism and that there is significant individual variability and thereby a susceptible sub-population to DMAA. Additionally, the peer-reviewed body of literature on other alpha-agonist sympathomimetics known to cause heat stroke (ecstasy, cocaine and amphetamine) confirm they do so through vasoconstriction and metabolic heat, 3) rate of error: all of the peer-reviewed and clinical studies relied on by Plaintiffs' experts have standard, published levels of statistical significance/error rate, 4) standards and controls: all of the Memphis studies as well as the Coyle study were

[21] *Gulf S. Insulation v. U.S. Consumer Prod. Safety Comm'n*, 701 F.2d 1137, 1146 (5th Cir. 1983) (rats received exposure over 100 times that found in average home with panel at issue.)
[22] ECF#196-5, Cantilena Dep. at 86:20-88:2.
[23]ECF#196-49, Baciu A, p. 121.

randomized, controlled clinical studies, accepted in peer-reviewed professional journals, and 5) general acceptance: the mechanism by which alpha-agonist sympathomimetics (of which DMAA has been proven to be) cause heat stroke is generally accepted in the scientific community as demonstrated by textbooks and the peer-reviewed literature. All of this research and this methodology predates litigation.

Thus, it was error to exclude the opinions.

B. The Magistrate Made Several Errors of Both Law and Fact

1. The Magistrate Did Not Consider Material Scientific Admissions from Defendants' Experts on Both the Ultimate Causation Opinions As Well As The Mechanism of Action

Critical causation issues were conceded by Defense experts. The concession as to mechanism was ignored. The mechanism of action of DMAA as an alpha-agonist vasoconstrictor was conceded by Defendants' toxicologist-expert, Dr. Joseph Rodricks.[24] Rodricks further admitted that DMAA mimics the activity of epinephrine.[25] Also not considered was that the Department of Defense, Army, textbooks and the FDA all agreed with Plaintiffs' experts on the mechanism of DMAA induced hyperthermia.[26] Thus, even if it was unreliable to use the Bloomer studies (see discussion *infra*) the Magistrate overstepped her role in excluding the opinion as to mechanism of action since the mechanism of action is not a factual issue in dispute. *See Collins v. Wayne Corp.*, 621 F.2d 777, 781 (5th Cir. 1980) (error to exclude the admissions from an opposing party's expert.)

Furthermore, it was the opinion of Cy Wilson, a USPLab's consultant hired for scientific analysis, long before litigation as to the death of Michael Sparling

[24] ECF#197-35, Rodricks Dep. (*Dube*) at 11:16-12:11, 178:23-179:11; ECF#197-36, Rodricks Dep. at 21:23-22:7.
[25] *Id.*
[26] ECF#276-21, DoD Rep. at 5; ECF#277-18-20;ECF#276-14-18 Bates 2720-21; ECF#276-60.

> Just between us, him taking the Jack3d prior to this test likely helped things along a bit by causing vasoconstriction and not allowing those blood vessels to dilate and reach the surface of the skin where they can help dissipate heat. . .[27]

An admission of the Defendants' own scientific consultant that Jack3d contributed to the death of Plaintiff Sparling and did so in the way that agrees with the expert opinions must be considered. In fact, where a party admission concedes ultimate causation there is no factual issue in dispute to begin with. Any factual finding to the contrary by the Magistrate exceeded the role as gatekeeper under *Daubert*.

These errors beg the question: how can the mechanism of action opinion be unreliable in the absence of evidence to the contrary?

2. Defense Argument and Cross-Examination is Not Evidence

There are several instances in which Defense argument or cross-examination suggested Plaintiffs' experts' methodology was not reliable without a single piece of evidence or scientific support. For example, the Defense argued that using the relative potencies in the Marsh dog study was unreliable without any scientific support. They offered no articles, textbooks or even their own experts to opine that using the dog model to calculate relative potencies was unreliable. In fact, Dr. Joseph Rodricks, the Defense toxicologist-expert, admitted that the dog model is a good comparison.[28] The comparison is valid because DMAA and epinephrine affect the cardiovascular system in both dogs and humans in the same way.[29] At any rate, pharmacologists/toxicologists should be able to testify as to fundamentals of their field without having to cite a specific article for every statement. This is especially the case where there was no evidence to the contrary. When the Magistrate made an independent factual finding that the

[27] ECF#276-41, Wilson Email at Bates # D0132991; ECF#277-41, Wilson Dep. at 26:11-25, 43:25-44:10, 123:24-124:9.
[28] ECF#197-36, Rodricks Dep. (*Sparling*) at 252:4-24.
[29] ECF#323, Hr'g Tr. at 12:22-17:7, 124:10-125:1, 133:2-135:2,126:25-127:10.

dog model was unreliable despite no evidence to the contrary and despite a party admission, she supplanted her scientific opinion for that of an expert in pharmacology. This was error.

3. The Magistrate Did Not Consider the Opinions as a Whole and Missed Numerous Bridges Between the Data and the Opinions

An expert's opinion need only rest on good grounds based on what is known and ordinarily should be subjected to the adversary process. *Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co.*, 161 F.3d 77, 85 (1st Cir. 1998). The entire body of evidence relied on by the expert should be taken into consideration in evaluating the reliability of the opinion, and the court should refrain from an "atomistic" approach that determines that each piece of evidence is insufficient, on its own, to support the expert's conclusion. *Milward v. Acuity Specialty Prods. Group, Inc.*, 639 F.3d 11, 23 (1st Cir. 2011); *In re Phenylpropanolamine (PPA) Products Liab. Litig.*, 289 F. Supp. 2d 1230, 1242 (W.D. Wash. 2003); *United States v. W.R. Grace*, 504 F.3d 745, 765 (9th Cir. 2007).

In this case, as in *Milward*, the Magistrate treated each evidentiary component atomistically as though the ultimate opinion was independently supported by each individual component. *Milward*, 639 F.3d at 23. For example, in holding that Dr. Cantilena's opinion is nothing more than class effects, the Magistrate states that Dr. Cantilena did not "account[] for any of the differences in sympathomimetics."[30] In fact he did. Dr. Cantilena's calculations bridge the gap the Magistrate said existed in the class effect discussion by accounting for differences in route of administration, pharmacokinetics, potency, and by providing an established mechanism of action.[31] The magistrate missed out on the big picture. There is no evidence that either Dr. Cantilena was not qualified to make the analysis or that the analysis was flawed.

[30] ECF#331 at p.34.
[31] ECF#323, Hr'g Tr. at 12:22-17:7.

4. The Magistrate Erred in Holding that the Opinions at Issue Were Nothing More than Opinions of Class Effect

The Magistrate misapplied Fifth Circuit law as to "class effects" in this case. The Fifth Circuit has acknowledged that class comparisons may be reliable and admissible. *Johnson v. Arkema, Inc.*, 685 F.3d 452, 460 (5th Cir. 2012); s*ee Moore v. Ashland Chem. Inc.*, 151 F.3d 269, 278-79 (5th Cir. 1998). Several courts have discussed mechanism of action or biologic plausibility as one way to bridge the analytical gap between the data and the expert's opinion. *E.g., In re Phenylpropanolamine (PPA) Products Liab. Litig.*, 289 F. Supp. 2d 1230, 1247-48[32]; s*ee also In re Zoloft (Sertraline Hydrocloride) Products Liab. Litig.*, 26 F. Supp.3d 466, 472 (E.D. Pa. 2014). The Magistrate did not consider these cases but instead relied upon *Wells v. SmithKline Beecham Corp.*, 601 F.3d 375, 379 (5th Cir. 2010), in which not only did the experts concede they were not offering an opinion as to causation, but they failed to explain why Requip could reliably be compared to other dopamine agonists in the class based on *Requip's specific characteristics*.[33] *Huss v. Gayden*, 571 F.3d 442 (5th Cir. 2009) does not answer the question whether Plaintiffs' experts can rely on the class-wide effects of sympathomimetics. Crucially, the expert in *Huss* gave no explanation as to the mechanism by which other sympathomimetics cause cardiomyopathy, let alone the one at issue. *See id.* at 458-59. Without that explanation the

[32] In the Phenylpropanolamine Multi-district Litigation (MDL), the court admitted an opinion using in part a methodology of comparing PPA to other sympathomimetics because the expert discussed the steps and research he used to compare them, a practice in accord with acceptable methods and procedure of science. *In re Phenylpropanolamine (PPA) Products Liab. Litig.*, *supra* at 1247-48. The MDL noted that while the defendants identified some of the problems of extrapolating or comparing PPA to other sympathomimetics, **they did not demonstrate that the practice failed to accord with accepted scientific methodology.** *Id*. at 1248. The court found that the reliance on biologic plausibility, comparison to like agents, case reports and adverse drug events, textbooks and clinical experience produced **cumulative evidence that was sufficient** under *Daubert*. *Id*.

[33] ECF#331 at p.34.

expert's concession that sympathomimetics can have dissimilar effects was fatal because he could not bridge the analytical gap from the class of sympathomimetics to the drug at issue. *See id.* Similarly, in *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1245-46 (11th Cir. 2005) the expert compared ephedrine to PPA but offered no proposed mechanism of how ephedrine or even PPA could cause *ischemic* stroke. Neither did Defendants offer a single case, reference, scientific article or opinion that using an established mechanism of action as a bridge to other drugs, about which more is known, is unreliable.

By contrast, in this case, Plaintiffs' experts are not merely asserting that because DMAA is a sympathomimetic and because other sympathomimetics have been demonstrated to cause hyperthermia DMAA can also cause hyperthermia. That would be a class effect case. Rather, Plaintiffs' experts have bridged the comparison using an established mechanism of action that DMAA has been demonstrated to have (vasoconstriction and metabolic heat) in peer-reviewed, randomized clinical trials in humans.[34] That mechanism (vasoconstriction and metabolic heat) is the same way in which other sympathomimetics (that everyone agrees cause hyperthermia) act to cause hyperthermia. Further, that mechanism is not theoretical but has been clinically proven at comparable levels (accounting for potency and pharmacokinetics) to that found in Plaintiff's antemortem blood. In short, while DMAA is in the sympathomimetic class it is the specific evidence of *how* it acts that forms the opinion.[35]

The Magistrate emphasized Dr. O'Brien's opinions that the Bloomer studies cannot be used for any purpose but ignored Dr. O'Brien's opinion the Bloomer studies can be used to show

[34] *E.g.*, ECF#321, Hr'g Tr. at 202:14-206:13.
[35] ECF#324, Hr'g Tr. at 5:9-6:4; ECF#321, Hr'g Tr. at 202:14-206:13.

mechanism of action.[36,37] And this is exactly how they were used: for mechanism of action, not ultimate causation. The Magistrate's approach also resulted in the exclusion of a human study of individuals exposed to DMAA in which there was a statistically significant increase in heat of one degree Fahrenheit which Dr. Coyle said could be the difference between life and death.[38] That the Bloomer studies did not share the conclusions of Plaintiffs' experts is irrelevant since they were not looking to determine whether DMAA caused hyperthermia or at outliers so they did not conclude one way or another whether DMAA could cause hyperthermia or whether there were pharmacodynamic outliers.[39]

The same error occurs with outliers in which the Magistrate concludes that outliers are only suggestive of association and thus not reliable.[40] Looking at the outliers in isolation, the Magistrate misses its role in the overall opinion: outliers demonstrate there are people who have stronger pharmacological reactions to DMAA, that they are more susceptible.[41] That the methodology of looking at the variable responses to a drug to show sensitivity in the general population is reliable the Magistrate needed to look no further than the Defense expert toxicologist Joseph Rodricks.[42] Nor did the Magistrate cite a single case that use of outliers is

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[36] ECF#331 at p. 36. The Magistrate also excludes use of the Bloomer studies based on sample size. However, that goes to the weight of the evidence. These are peer-reviewed studies. It is reliable to use them and as discussed *supra* Defendants' experts also relied on them. Indeed the Magistrate cites no case, other than *Gulf S.*, 701 F.2d at1146 which looks at toxic exposures in rats at higher levels than those to which humans are exposed, that requires a per se exclusion of studies that, although peer-reviewed and show statistical significance in humans using doses comparable to
marketed products, are too small.

[37] ECF#276-49, O'Brien Rep. at ¶ 31; ECF#276-23, O'Brien Dep. at 118:13-119:2.

[38] ECF#223, Exh. V; ECF#276-54, Coyle Dep. at 224:20-225:24.

[39] ECF#196-34-37; ECF#196-5, Cantilena Dep. at 149:4-6.

[40] ECF#331 at p. 39.

[41] ECF#196-5, Cantilena Dep. at 160:22-161:25, 262:15-263:9. Moreover outliers are not central to the opinion. They just answer the question why everyone does not get hyperthermia.

[42] ECF#197-36, Rodricks Dep. at 183:17-184:5, 224:11-227:9.

unreliable. Again, not a single piece of contrary evidence was produced. Finally, the Magistrate incorrectly stated that Dr. Cantilena did not explain how Plaintiff was an outlier.[43]

5. The Opinions Did State That DMAA is Capable of Causing Hyperthermia in the General Population

Throughout her opinion the Magistrate concluded the experts do not offer opinions that DMAA causes or is capable of causing hyperthermia in the general population.[44] However, the Magistrate does not cite a single case that a general causation opinion that says a drug is capable of causing a particular injury in the general population but that only susceptible people actually develop the injury is unreliable. It is generally accepted (and undisputed) in adjudication of causality for drugs there is a susceptible sub-population of persons who actually develop injuries because the effect of drugs differs among individuals.[45] But that susceptible population exists within the general population. General population does not mean all people. An expert does not have to opine that a drug *actually* causes harm in everyone only that it is *capable* of harming people in the general population. Dr. Rusyniak, a nationally recognized expert in sympathomimetic-induced hyperthermia, testified that DMAA increases the risk of hyperthermia in everyone, which is consistent with the fact that despite the elevated risk, not everyone will suffer hyperthermia.[46] As such, Plaintiffs' experts did not say that DMAA is not *capable* of causing hyperthermia in the general population; rather, they said that only susceptible people actually develop it.[47] Furthermore, the experts opined that the reaction is idiosyncratic, which by

[43] ECF#323, Hr'g Tr. at 42:19-43:5.
[44] ECF#331 at pp. 36-39, 51.
[45] ECF#196-5, Cantilena Dep. at 45:24-46:6, 89:11-17, 204:1-5; ECF#196-46, Buxton I.L, Benet L.Z. at p. 37; ECF#196-42 through 44, Westfall T.C & Westfall D.P. at 299; Exh. 196-45, Blumenthal D.K at p. 49.
[46] ECF#321, Hr'g Tr. at 127:19-128:6.
[47] *E.g. id.* at 204:10-205:4.

definition means one cannot predict who will have the reaction.[48] In other words, because DMAA is capable of causing hyperthermia in anyone and clinicians cannot predict prior to ingestion who will develop hyperthermia, DMAA is necessarily capable of causing hyperthermia in the general population. A nearly identical opinion has been found reliable.[49,50]

The Magistrate placed too much focus on the literal meaning of "general population." The Magistrate's approach essentially bars any opinion in any drug case in which the drug did not cause the particular injury in everyone who took it. Since the adverse drug reactions of nearly all drugs, with the exception of poisons, are unpredictable such a doctrine would effectively expand *Daubert* to prohibit expert opinions in any drug case.

6. The Magistrate Focused on the Conclusions Rather than the Methodology

The Magistrate wandered far from a focus on the methodology. For example, the Magistrate imposed additional hurdles to admissibility, including proof that a study concludes the ultimate opinion that DMAA causes hyperthermia in the general population, that a study even though statistically significant needs some minimum sample size, that it is unreliable to use a study which does not reach a conclusion on the issue of ultimate causation, that statistical analysis is a prerequisite to using outliers despite the fact the methodology requires a clinical assessment, that an opinion is only reliable if created before litigation, and that only peer-reviewed methodologies are reliable.[51] The Magistrate apparently would accept a clinical study showing DMAA caused hyperthermia in humans and nothing less. By doing so, the Magistrate

[48] ECF#324, Hr'g Tr. at 64:3-7.
[49] *E.g.*, ECF#197-39, *In re: Ephedra Products Liability Litigation (MDL 1598)*, Case No. 04 MD 1598 JR at *25-28 (S.D.N.Y 2005).
[50] The opinion was written by Hon. Judge Jed S. Rakoff who is a sitting member of the Committee on the Development of the Third Edition of the Reference Manual on Scientific Evidence.
[51] ECF#331 at pp. 36-41.

unfortunately went far beyond assessing the methodologies and weighed the evidence.

7. Evidence Was Provided that the Calculations Were Reliable

There appears to be confusion as to what the Marsh dog data was used for. Dr. Cantilena wanted to compare the relative effects of DMAA to epinephrine since the Coyle study measured actual cutaneous vasoconstriction and the increased heat resulting therefrom in exercising humans.[52] He wanted to find out if the amount of DMAA to which Sparling was exposed could be expected to have a substantially comparable effect as the epinephrine.[53] The existing studies in the field of comparing DMAA to epinephrine were conducted by Marsh group in connection with the development of DMAA as a drug by Eli Lilly. Those studies were only conducted in dogs. However, all parties agree, including Dr. Rodricks, Dr. Cantilena and Dr. Mills (see discussion infra), that dogs are a good human comparator for measurements of the cardiovascular response. Moreover, the doses of DMAA given to dogs were not used to show that similar levels are toxic in humans. It was merely used to show the *relative potency* between DMAA and epinephrine. Thus, while differences in absorption, distribution and metabolism between animals and humans should be considered that applies to comparing toxic doses between humans and animals. Reference Manual for Scientific Evidence (Third Ed.) p.679.

The Magistrate also erred when she found that Dr. Cantilena did not explain the significance of the 30% difference in the calculation between the Coyle study and the level of DMAA found in Sparling.[54] Dr. Cantilena said the DMAA found in Sparling on autopsy that he used was the lowest, most conservative estimate (i.e. it underestimated the true serum level) because it assumed Sparling received no I.V. fluid, which would have made his serum level of

[52] ECF#323, Hr'g Tr. at 12:22-17:7, 124:10-127:10, 133:2-135:2.
[53] *Id.*
[54] ECF#331 at pp.40-43.

DMAA much higher.[55] Thus, given that in fact the levels would be much closer Dr. Cantilena testified 30% was "substantially similar."[56] Moreover, the Defense provided not a single study, expert opinion or any shred of scientific evidence that the 30% gap in relative potencies is not substantially equivalent when comparing pharmacodynamics (drug effects). In cases excluding opinions based on animal studies the dose was considerably higher (on the order of 100 times or more) not within 30%.[57] The Magistrate made an independent scientific determination that these calculations were unreliable despite this eminent pharmacologist's sound methodology. She did so without any evidence. Accepting cross-examination or argument from the Defense as having some factual or scientific basis with no evidence subverts the purpose of Rule 702.

8. The Magistrate Ignored Peer-Reviewed Medical Literature that Jack3d Killed Plaintiff

The Magistrate found use of case reports by Plaintiffs' experts was unreliable because they involved different drugs and different injuries.[58] However, the Magistrate ignored the Eliason article which concluded that DMAA is capable of causing hyperthermia and that Sparling's death is consistent with his use of Jack3d.[59] The opinion of these military experts that DMAA is capable of causing hyperthermia and that Sparling's death was consistent with his use of DMAA should have been considered as evidence that the methodologies and opinions of Plaintiffs' experts were reliable and sound.

[55] ECF#232, Hr'g Tr. at 141:22-143:5, 37:24-39:11.
[56] *Id*.
[57] *E.g, Gulf S. Insulation*, 701 F.2d at 1146 (rats received exposure over 100 times that found in average home with panel at issue.)
[58] ECF#331 at pp.44-45.
[59] ECF#196-25, Eliason M.J.

III. CONCLUSION

Given the considerable peer-reviewed literature on DMAA and the accepted methodologies used by the experts, as well as the mistakes of fact and errors of law discussed above, Plaintiffs respectfully request this Court overrules the Magistrate's Order Strike the testimony of Dr. Cantilena, Dr. Rusyniak and Dr. Mills.

Respectfully submitted,

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